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(54) Dihydrospirorenon als Antiandrogen

Use of dihydrospirorenone as an anti-androgen

Utilisation de la dihydrospirorénone comme agent antiandrogène

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(56) Entgegenhaltungen:
EP-A- 0 253 607
DE-A- 3 022 337
US-A- 4 347 245

- **KLINISCHE WOCHERSCHRIFT, Band 64, Nr. 16, 1986, Seiten 732-737; M. BREINER et al.: "Inhibition of androgen receptor binding by natural and synthetic steroids in cultured human genital skin fibroblasts"**

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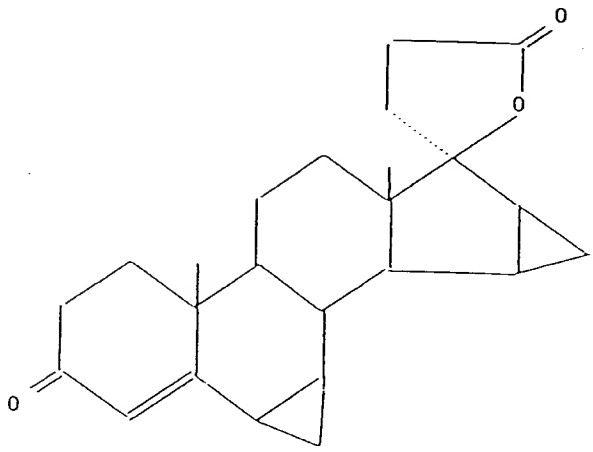
The present invention relates to the use of the compound of formula I



(I)

in the preparation of a medicament.

Compound I (dihydrospirorenone) is described in DE-A 26 52 761 inter alia as a diuretic of the aldesterone antagonist type.

It is apparent from DE-A 30 22 337 that, at doses at which the anti-aldosterone activity becomes evident, compound I also has a clear gestagenic activity. Compound I may therefore be used alone or in combination with oestrogens in contraceptive preparations.

According to DE-A 30 22 337, those preparations should be used in women who want contraception and suffer from high blood pressure or in whom taking oral contraceptives results in an increase in blood pressure. Hormone contraception thus became possible even for women predisposed to increased blood pressure.

A combination preparation for replacement therapy and contraception for women before the menopause (from about the age of 40) is known from EP-A 0 253 607. That combination preparation comprises an oestrogen from the

group

17β-oestradiol,
ethinyloestradiol, and
mestranol,

and a gestagen from the group

laevonorgestrel,
gestoden,
desogestrel,
2-ketodesogestrel, and
norethindrone.

A composition selected thus should balance hormone irregularities in the transition phase of the pre-menopause and help to alleviate the complaints caused in that phase as a result of hormone changes in the female body. At the same time, such a composition provides the contraceptive protection that is still necessary at that age.

For various known reasons and as a result of the increase in the incidence of contraindications with increasing age, taking hormone contraceptives is recommended only for women of up to approximately 35 years, with the result that hormone treatment in the pre-menopause and replacement therapy in the climacteric using doses that simultaneously act as contraceptives may be regarded as problematic.

In addition to those conditions that justify a contraindication, there are often observed in women of advanced years androgenisation phenomena, such as, for example, growth of facial hair, deepening of the voice and also blemished skin; an increase in blood pressure is often also noted.

It has now been found that the compound of formula I has,

surprisingly, in addition to its gestagenic and anti-aldosterone activity, a strong anti-androgenic activity component at doses that permit that compound to be formulated in the form of oral contraceptives. Dihydrospirorenone has approximately the same strength of anti-androgenic activity as the standard compound, cyproterone actetate (equal maximum activity). (Animal model: juvenile, castrated and testosterone-replaced male rat; methods described in: Methods in Hormone Research, Editor: R.I. Dorfman, Academic Press, New York, London, 1969, pp. 241; or Androgens and Antiandrogens, Editors: L. Martin and M. Motta, Raven Press, New York, 1977, pp. 163).

The present invention accordingly relates to the use of the compound of formula I in the preparation of a medicament that is suitable simultaneously for the treatment of hormone irregularities in the pre-menopause (stabilisation of the cycle) and for hormone replacement therapy in the climacteric and for the treatment of androgen-induced disorders and for contraception.

A medicament produced according to the invention may, of course, also be used exclusively for the treatment of androgen-induced disorders, or for the treatment of such disorders with simultaneous contraception and/or treatment of hormone irregularities in the pre-menopause or for the treatment of such disorders with simultaneous contraception and/or for hormone replacement therapy in the climacteric or for the treatment of such disorders and/or treatment of hormone irregularities in the pre-menopause and/or for hormone replacement therapy in the climacteric.

Preferably an oestrogen is used together with a compound of formula I. Whether a synthetic or a natural oestrogen

is used depends upon whether the contraceptive activity or the replacement effect is of more importance; in the former case, ethinyloestradiol or another synthetic oestrogen is preferred; in the latter case, such a medicament should contain a natural oestrogen.

In all cases, however, such a medicament provides a middle-aged women (approximately from 35 to 55 years) with stabilisation of her menstrual cycle and also with the contraception that is still indispensable at that age whilst simultaneously having a positive effect upon androgen-induced disorders. The medicament is, of course, also suitable for younger women, especially for those who have a particular predisposition to high blood pressure and suffer from androgenisation phenomena. Such a use is only now possible because the compound of formula I combines simultaneously a gestagenic, anti-aldosterone and strong anti-androgenic activity. Hitherto, no substance was known that had those three properties simultaneously.
The dosage of the compound of formula I should be from 0.5 to 50 mg daily, preferably from 1 to 10 mg daily.

There come into consideration as oestrogens all hitherto customary oestrogens. The oestrogen used should be administered preferably in such doses that the amount of oestrogen used according to the invention is equal to an amount corresponding to the administration of from 0.02 to 0.04 mg of 17α-ethinyloestradiol, or from 0.5 to 4.0 mg of oestradiol valerate, daily. Suitable oestrogen components are inter alia also 17α-ethinyloestradiol esters and ethers and also, for example, esters of 17α-ethinyl-7α-methyl-1,3,5(10)-oestratriene-1,3,17β-triol (German Patent Specification 1 593 509 and DE-OS 2 818 164). Also suitable are the 14,17β-ethano-14β-oestratrienes described in DE-A 36 28 189. The oestrogenic and

gestagenic active ingredient components are preferably administered together orally; they may, however, also be administered separately and/or parenterally or transdermally.

The preparations according to the invention based on 6β,7β;15β,16β-dimethylene-3-oxo-4-androsten-[17(β-1']-perhydrofuran-2'-one are formulated in a manner known per se by processing the active ingredient, optionally in combination with an oestrogen, with the carriers, diluents, optionally taste correctives etc. customary in galenic pharmacy and converting the mixture into the desired form of administration. For the preferred oral administration, there come into consideration especially tablets, dragées, capsules, pills, suspensions and solutions. Suitable for parenteral administration are especially oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil. Solubilizers, such as, for example, benzyl benzoate or benzyl alcohol, may be added to increase the solubility.

The formulation of some preparations is illustrated hereinafter in greater detail with reference to various Application Examples.

Example 1

20.0 mg of 6β,7β;15β,16β-dimethylene-3-oxo-4-androsten-[17(β-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17α-ethinyloestradiol are mixed homogeneously with 140.45 mg of lactose, 59.5 mg of corn starch, 2.0 mg of Aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate, and the mixture is compressed, without previous granulation, to form a tablet having a final weight of 225 mg.

Example 2

Analogously to Example 1, 10 mg of 6β,7β;15β,16β-dimethylene-3-oxo-4-androsten-[17-(β-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17α-ethinyloestradiol are compressed [with 150.45 mg of 17α-ethinyloestradiol][1] with 150.45 mg of lactose, 59.5 mg of corn starch, 2.0 mg of Aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate to form tablets having a final weight of 225 mg.

Example 3

Analogously to Example 1, 20 mg of 6β,7β;15β,16β-dimethylene-3-oxo-4-androsten-[17-(β-1')-spiro-5']-perhydrofuran-2'-one are compressed with 140.5 mg of lactose, 59.5 mg of corn starch, 2.0 mg of Aerosil, 2.5 mg of polyyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate to form tablets having a final weight of 225 mg.

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[1] Translator's note:
The words contained in the parenthesis would, in context, appear to have been included in the German in error.

Patent Claims

1. Use of dihydrospirorenone in the preparation of a medicament that is suitable for the simultaneous treatment of

a) aldosterone-induced disorders, and
b) hormonal irregularities (stabilisation of the cycle), and
c) for contraception, and
d) for the treatment of androgen-induced disorders.

2. Use of dihydrospirorenone in the preparation of a medicament that is suitable for the simultaneous treatment of

a) aldosterone-induced disorders, and
b) androgen-induced disorders, and
c) for hormone replacement therapy in the menopause.

3. Use according to either claim 1 or claim 2, wherein the aldosterone-induced disorder is high blood pressure.

4. Use of dihydrospirorenone according to either claim 1 or claim 2 in combination with an oestrogen.

5. Use according to claim 4, wherein the oestrogen is a synthetic oestrogen.

6. Use according to claim 4, wherein the oestrogen is a natural oestrogen.

7. Use of the combination according to either claim 1 or claim 4 in the preparation of a medicament for pre-menopausal women.